Refractory intracranial hypertension: the role of decompressive craniectomy

Martin Smith¹,² MBBS, FRCA, FFICM

¹Neurocritical Care Unit, The National Hospital for Neurology and Neurosurgery
University College London Hospitals, Queen Square, London, UK.
Email: martin.smith@ucl.ac.uk
²UCLH/UCL National Institute for Health Research Biomedical Research Centre

Corresponding author
Martin Smith
Department of Neuroanaesthesia and Neurocritical Care
The National Hospital for Neurology and Neurosurgery
University College London Hospitals
Queen Square
London WC1N 3BG
United Kingdom

Tel: +44 (0)20 3448 4711
Email: martin.smith@ucl.ac.uk

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Abstract

Raised intracranial pressure (ICP) is associated with worse outcomes after acute brain injury, and clinical guidelines advocate early treatment of intracranial hypertension. ICP-lowering therapies are usually administered in a stepwise manner, starting with safer first-line interventions while reserving higher risk options for patients with intractable intracranial hypertension. Decompressive craniectomy is a surgical procedure in which part of the skull is removed and the underlying dura opened in order to reduce brain swelling-related raised ICP; it can be performed as a primary or secondary procedure. After traumatic brain injury secondary decompressive craniectomy is most commonly undertaken as a last-tier intervention in a patient with severe intracranial hypertension refractory to tiered escalation of ICP-lowering therapies. Although decompressive craniectomy has been used in a number of conditions, it has only been evaluated in randomized controlled trials after traumatic brain injury and acute ischemic stroke. After traumatic brain injury decompressive craniectomy is associated with lower mortality compared to medical management but with higher rates of vegetative state or severe disability. In patients with stroke-related malignant hemispheric infarction hemicraniectomy significantly decreases mortality and improves functional outcome in adults younger than 60 years of age. Surgery also reduces mortality in those older than 60 years, but results in a higher proportion of severely disabled survivors compared to medical therapy in this age group. Decisions to recommend decompressive craniectomy must always be made not only in the context of its clinical indications but also after consideration of an individual patient’s preferences and quality of life expectations. This narrative review discusses the management of intractable intracranial hypertension in adults, focusing on the role of decompressive craniectomy in patients with traumatic brain injury and acute ischemic stroke.
Introduction

The management of patients with acute brain injury is based on the central concept that prevention of secondary injury is associated with improved clinical outcomes. There are multiple causes of secondary brain injury including metabolic, excitotoxic and inflammatory responses that are exacerbated by systemic and intracranial physiological insults which, together, cause or worsen cerebral hypoxia and ischemia. \(^1\) Raised intracranial pressure (ICP) and reduced cerebral perfusion pressure (CPP) are long established and important causes of secondary brain injury that are associated with a greater burden of cerebral ischemia and worsened clinical outcomes. \(^2,3\) This narrative review discusses the management of intractable intracranial hypertension in adults, focusing on the role of decompressive craniectomy in patients with traumatic brain injury (TBI) and acute ischemic stroke (AIS).

Intracranial hypertension, monitoring and outcomes

The rigid, non-compliant nature of the skull means that worsening brain edema or an expanding intracranial hematoma results in an increase in ICP which, in turn, causes a reduction in CPP, cerebral blood flow and oxygenation. \(^4\) This establishes a vicious cycle of brain ischemia, worsening edema and further increases in ICP which, if not interrupted, can lead to brain herniation and death. \(^5\) When intracranial compensatory reserves become exhausted the relationship between intracranial volume and pressure is exponential, such that ICP increases rapidly and substantially as a result of small incremental increases in space-occupying edema/hemorrhage or intracranial blood volume. This explains the often rapid clinical deterioration in patients with reduced intracranial compliance.

Intracranial hypertension has been associated with increased mortality in large cohort studies of TBI \(^2,6,7\), establishing it as a marker of disease severity. It is the burden of intracranial
hypertension (duration as well as severity) that is related to poor outcomes\textsuperscript{8-10}, and all clinical guidelines advocate the early treatment of raised ICP after TBI.\textsuperscript{11,12} Despite this there is little evidence that monitoring and managing ICP improves patient outcomes.\textsuperscript{13} The only randomized clinical trial evaluating the utility of ICP monitoring in TBI - the Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure (BEST:TRIP) study - found similar three- and six-month outcomes following treatment guided by ICP monitoring compared to treatment guided by imaging and clinical examination in the absence of ICP monitoring.\textsuperscript{14} The number of days of brain-directed therapy was lower in the ICP monitored group, although the median length of ICU stay was similar in the two groups. BEST:TRIP did not test the value of ICP monitoring \textit{per se} but rather the efficacy of the management of intracranial hypertension identified by two different methods. Since both treatment approaches provided satisfactory outcomes despite the absence of ICP monitoring in one, BEST:TRIP challenges the established practice of maintaining ICP below a universal and arbitrary threshold.\textsuperscript{15} While ICP and CPP are crucially important and routinely monitored variables after TBI, they provide no assessment in an individual patient of the adequacy of cerebral perfusion and therefore of the risk of brain ischemia.\textsuperscript{3} Cerebral ischemia can occur despite ICP and CPP being within accepted thresholds for normality, and will be undetected when therapy is guided by ICP/CPP monitoring alone.\textsuperscript{16,17} Individualized interpretation of ICP (and CPP) values, in association with other monitored variables, such as ICP waveform analysis of autoregulatory status and cerebral oxygenation and metabolism, allows individualized treatment decisions to be guided by monitored changes in physiological state rather than a generic ‘one size fits all’ target for ICP (and CPP).\textsuperscript{18,19}

Clinically significant cerebral edema and intracranial hypertension develops in a small but significant proportion of patients with AIS, typically those with distal internal carotid artery
occlusion or proximal occlusion of the middle cerebral artery (MCA). The latter is often referred to as ‘malignant MCA syndrome’ because it is a life-threatening event associated with clinical deterioration within 48 hours of stroke onset in two-thirds of affected patients, and a mortality rate of almost 80% if untreated and in excess of 50% despite maximal medical management. In the awake and cooperative patient, regular neurological examination and cranial imaging are the cornerstones of detecting deterioration after AIS, and remain the focus of clinical decision-making. Hypodensity involving greater than 50% of the MCA territory or worsening midline shift on computed tomography (CT) imaging are highly predictive of the development of malignant MCA syndrome, but neuromonitoring-guided management has unproven benefits. ICP monitoring is often used in patients with large space-occupying infarcts and edema, but measured ICP values may be normal despite large ischemic tissue volumes. Because the majority of stroke patients are not sedated, non-invasive neuromonitoring methods might have wider applicability. Unfortunately they are currently insufficiently reliable for routine clinical use.

**Treatment of intracranial hypertension**

The most recent guidance from the Brain Trauma Foundation recommends ICP-lowering therapy after TBI when ICP rises above 22 mmHg. Modern neurocritical care management incorporates tiered ICP- and CPP-guided strategies that include both medical and surgical interventions (table 1). ICP-lowering therapies are usually administered in a stepwise manner, starting with safer first-line interventions while preserving higher risk options for patients with intractable intracranial hypertension, multimodal neuromonitoring evidence of brain hypoxia/ischemia or cerebral metabolic distress, or those at imminent risk of herniation. The requirement for escalation of treatment for intracranial hypertension implies more severe
disease and is associated with poorer prognosis; the relative risk of death is increased by 60% in patients in whom escalation to stage 2 ICP-lowering interventions is necessary.\

General first-tier measures, including timely removal of space-occupying traumatic lesions, should be implemented in all at risk patients, with escalation to second-tier therapies if ICP remains above 22mmHg (table 1). Osmotic agents are widely used to reduce raised ICP, and mannitol is recommended by consensus guidelines for the acute treatment of monitored increases in ICP although it has never been subject to a randomized comparison against placebo. Hypertonic saline is also an effective ICP-lowering intervention and is associated with fewer side effects than mannitol, but comparisons between the two have not demonstrated superiority of one over the other. If second-tier measures fail to control ICP, third line interventions such as therapeutic hypothermia are initiated (table 1). The recent Eurotherm3235 trial randomized TBI patients with ICP > 20 mmHg resistant to first tier treatments to standard second tier therapy (osmotherapy) or standard care plus hypothermia (32-35°C). The study was suspended early because of higher mortality and worse functional outcomes in the hypothermia group. While Eurotherm3235 provides evidence against the early use of hypothermia to lower ICP after TBI, it does not address its role in the management of refractory intracranial hypertension. Most algorithm-based approaches introduce cooling only when few alternatives to control ICP remain, primarily in an attempt to limit the use of high-risk fourth-tier interventions such as barbiturate infusion and decompressive craniectomy.

Barbiturates reduce cerebral metabolism and blood flow, leading to a proportional decrease in cerebral blood volume and ICP. They are associated with serious side effects including cardiac depression, arterial hypotension and increased risk of infection, and their efficacy in
controlling refractory intracranial hypertension and improving outcomes is uncertain. Barbiturate infusion should be considered only when other therapies have been tried and failed to control ICP, and after careful assessment of the balance between potential benefits (limited) and use-associated risks (high).

Treatment options for malignant MCA infarction include general measures to limit space-occupying edema, but these are often ineffective. Osmotherapy has not been shown to improve outcomes after AIS, and steroids have no role. A number of small studies have demonstrated the safety and feasibility of moderate hypothermia after AIS, but potential beneficial effects on outcome remain unproven.

**Decompressive craniectomy**

Decompressive craniectomy is a surgical procedure in which part of the skull is removed and the underlying dura opened. From a physiological perspective it overcomes the rigid and non-compliant nature of the skull and dura mater and thereby leads to a reduction in ICP. In patients with worsening brain edema it effectively provides additional space for the swollen brain and mitigates the risk of further ICP elevations and brain herniation. In addition to brain tissue volume and the presence of mass lesions, ICP is also related to intracranial blood volume and therefore to the balance between arterial inflow and venous outflow. Although the venous contribution to ICP is often overlooked, restrictions to venous outflow lead to immediate and dramatic changes in intracranial blood volume and ICP which can be as significant in terms of ICP elevation as intracranial mass lesions or cerebral edema. Diffuse brain swelling can lead to generalised venous compression and a cycle of venous hypertension, more brain swelling and worsening venous compression, and further increases in venous pressure and ICP. Although this phenomenon has historically been associated with
idiopathic intracranial hypertension, it has recently been described after TBI when alleviation of venous sinus compression might have contributed to the ICP-reducing effects of decompressive craniectomy.\textsuperscript{33}

There is evidence dating from ancient civilisations of interventions to decompress the skull but the modern surgical technique was first described by Thomas Kocher in 1901 and subsequently in 1908 by Harvey Cushing who reported substantial mortality reductions in head-injured patients treated with subtemporal decompressive craniectomy.\textsuperscript{34} Advances in neuroimaging and neurocritical care during the 1980s and 1990s, including the widespread adoption of monitoring-guided protocols for ICP management, led to renewed interest in decompressive craniectomy as a means to control ICP and the publication of case series and uncontrolled studies that demonstrated potential outcome benefits.\textsuperscript{35} Although it has been used and investigated in a number of conditions, decompressive craniectomy has only been evaluated in randomized controlled trials after TBI and AIS.

Decompressive craniectomy can be performed as a primary or secondary procedure. In primary decompression a part of the skull (the craniotomy bone flap) is not replaced after evacuation of an intracranial mass lesion.\textsuperscript{32} It is most commonly used after evacuation of an acute subdural hematoma (ASDH) either because brain swelling prevents replacement of the bone at the end of surgery or as a pre-emptive measure because of concern that substantial swelling is likely to occur in the early postoperative period. A non-randomized cohort study demonstrated a lower mortality rate in patients undergoing primary decompressive craniectomy compared to craniotomy and bone-flap replacement after evacuation of an ASDH,\textsuperscript{36} but there is no high quality evidence to recommend this approach and considerable practice variation amongst neurosurgeons.\textsuperscript{37} The Randomised Evaluation of Surgery with
Craniectomy for patients Undergoing Evacuation of Acute Subdural Haematoma (RESCUE-ASDH) trial is a multicentre, pragmatic randomized trial comparing the effectiveness of primary decompressive craniectomy versus craniotomy and bone-flap replacement after evacuation of an ASDH in adult head-injured patients (http://www.rescueasdh.org/); it will complete recruitment in 2019.

Secondary decompressive craniectomy is most commonly undertaken as a last-tier (life-saving) intervention in a patient with severe intracranial hypertension refractory to tiered escalation of interventions to control ICP. More rarely, it has been used as a second-tier therapy to control lower levels of intracranial hypertension. There are three main approaches to secondary decompressive craniectomy – bifrontal craniectomy, unilateral hemicraniectomy and bilateral hemicraniectomy – and the reader is referred elsewhere for a detailed description of the different surgical techniques. Importantly, the craniectomy should be of sufficient size to allow effective reduction of ICP and the dura opened widely to maximize ICP control. Surgical practices with regard to decompressive craniectomy in the management of TBI vary internationally, and this creates difficulty when comparing the results of published studies.

Decompressive craniectomy is major surgery and associated with significant early and late complications including seizures, subdural hygroma, hydrocephalus, and infection. The majority of patients also require a subsequent cranioplasty for brain protection, restoration of the original skull contour for cosmetic reasons and, in some cases, to alleviate neurological symptoms attributable to the syndrome of the trephined. Cranioplasty can itself be associated with a number of complications including intracranial hemorrhage, infection, seizures and problems with wound healing. Sudden death secondary to cranioplasty-related acute
brain swelling has also been reported. The complications and potential benefits of cranioplasty have not been systematically studied in clinical trials of decompressive craniectomy.

**Decompressive craniectomy and traumatic brain injury**

The last decade has seen intense debate about the relative merits and disadvantages of secondary decompressive craniectomy in the management of intracranial hypertension after severe TBI. Non-randomized trials and controlled trials with historical controls reported substantial ICP reductions and some evidence of improved outcomes after craniectomy, but with concerns of survival with severe disability. Two recent randomized clinical studies – the Decompressive Craniectomy (DECRA) study and the Randomised Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intracranial Pressure (RESCUEicp) study – systematically investigated decompressive craniectomy to control elevated ICP after severe TBI. In both, the Extended Glasgow Outcome Scale (GOS-E) score was used as a primary and secondary outcome measure. GOS-E assesses functional independence, work, social and leisure activities, and personal and social relationships using an 8-point scale ranging from 0 (death) to 8 (upper good recovery, i.e. no injury-related problems). GOS-E 4 (upper severe disability) or better was used to categorize favourable outcome in both studies. An individual categorized as GOS-E 4 is independent at home (or can be left alone for at least 8 hours) but requires assistance outside the home.

The DECRA study randomly assigned 155 adults within 72 h of severe diffuse TBI to either bifrontal decompressive craniectomy or standard care if they developed intracranial hypertension (defined as ICP greater than 20 mmHg for more than 15 minutes in a one-hour period) refractory to first-tier therapies. Surgical decompression was associated with lower
ICP than medical treatment, fewer hours of ICP > 20 mmHg after randomization, and shorter intensive care unit length of stay. Mortality was similar in the two treatment groups (19% and 18%), but unfavourable outcome (composite of death, vegetative state or severe disability, GOS-E 1-4) was higher in the craniectomy compared to medical treatment group (70% vs. 51%, odds ratio 2.21, p=0.02). While the two groups were well-matched for most variables, there was a higher proportion of patients with bilateral unreactive pupils in the decompressive craniectomy group (27% vs. 12 % in the medical treatment group, p=0.04). Following post hoc adjustment for baseline pupil reactivity there was no difference in the rates of unfavourable outcomes between the two treatment groups. In contrast to earlier (uncontrolled) studies, DECRA provided no evidence of benefit from surgical decompression over medical management when craniectomy is used as a second tier intervention in patients with modestly raised ICP. It therefore increased rather than resolved the controversy about the indications, timing and selection of patients for decompressive craniectomy after TBI.38

The DECRA study has been criticised for several reasons. First, the ICP threshold (ICP > 20 mmHg for > 15 min in a single hour) is considered by many experts to be an inappropriate trigger for major surgical intervention.49 They argue that such modest levels of ICP would not lead to escalation to second-tier medical therapies in many centers, and that the short period of modestly raised ICP did allow sufficient time for its optimization with first-tier therapies. Second, the DECRA study included only a small subset of TBI patients (those without intracranial mass lesions) and recruited only 155 of 3478 (4.5%) of those assessed for eligibility. Finally it has been argued that the choice of surgical technique (bifrontal craniectomy without division of the sagittal sinus and falx) limited the procedural efficacy for lowering ICP.50 Although the authors mounted robust responses to these criticisms,51 the impression that DECRA does not reflect ‘real-life’ clinical practice persists.38 Despite this,
the results of the DECRA study are important. Confirmation that there is no role for decompressive craniectomy as an early intervention to treat intracranial hypertension gives clinicians confidence to escalate to second and third tier ICP-lowering medical therapies despite the increasing risk of treatment-related complications, while limiting surgical decompression to last-tier intervention.

Subsequently the RESCUEicp study investigated the effectiveness of bifrontal or unilateral hemicraniectomy as a last-tier therapy for severe, sustained and refractory intracranial hypertension after TBI. In this multi-center study, 408 patients were randomised to decompressive craniectomy or continuing medical therapy if ICP exceeded 25 mmHg for at least 1 h and was refractory to tiered escalation of ICP lowering therapies. Barbiturate infusion was not allowed prior to randomization but was an option to control ICP in the medical treatment arm following randomization. Surgical decompression was associated with lower ICP than medical treatment and fewer hours of ICP > 25 mmHg after randomization. Compared to medical management, decompressive craniectomy resulted in lower mortality at six months (48.9% vs. 26.9% respectively, p < 0.01), but higher rates of vegetative state and severe disability (GOS-E 2-4, p < 0.01). The rates of moderate disability and good recovery were similar in the two groups. At 12 months, a higher percentage of patients in the surgical group had a favourable outcome compared to those in the medical group (45.4% vs. 32.4%, p = 0.01). The authors estimated that there were 22 more survivors for every 100 patients treated with craniectomy compared to medical treatment at 6 months, but only 8 (36%) had a favourable outcome (GOS-E 4-8); 6 (27%) were in a vegetative state (GOS-E 2) and 8 (36%) remained dependent on others for care (GOS-E 3, lower severe disability). At 12 months, 13 of 22 survivors (59%) had favourable outcomes, 5 (23%) were in a vegetative state and 4
(18%) had lower severe disability. The absolute 6 and 12 month outcomes reported in the RESCUEicp study are summarized in table 2.

RESCUEicp was a pragmatic study which incorporated a widely accepted definition of refractory intracranial hypertension. It also studied a more representative cohort of TBI patients because it included those with intracranial hematomas as well as diffuse brain injury. However, like all studies it has limitations. First, patients in the surgical group underwent either bifrontal (63%) or unilateral (37%) craniectomy based on CT imaging findings but at the operator’s discretion. An analysis according to the type of surgery was not performed and this would be of interest because of the current variation in surgical practices. Second, a relatively large proportion of patients (37%) in the medical group underwent craniectomy because of failure of barbiturates to control ICP adequately. In contrast only 9% of surgical patients required addition of barbiturates because of failure of craniectomy to control ICP. These treatment crossovers had no impact on the reported outcomes which were analysed on an intention to treat basis, but they do reinforce clinical experience that maximal medical therapy does not adequately control ICP in many patients. Although RESCUEicp was an international study, more than 70% of patients were recruited from the United Kingdom.

**Decompressive craniectomy and stroke**

The role of decompressive craniectomy in malignant MCA infarction has been widely investigated. Unlike in studies of TBI, stroke studies often use the modified Rankin scale (mRS) as the outcome measure. mRS ranges from 0 to 6, with 0 indicating no symptoms and 6 death. Individuals with a score of 0, 1, or 2 are functionally independent, whereas those with mRS 4 and 5 require assistance for most daily needs.\(^{52}\)
Early evidence from uncontrolled case series confirmed a survival benefit of hemicraniectomy after malignant MCA infarction, but effects on functional outcome were less clear.\textsuperscript{53} Three small European randomized trials - the Decompressive Craniectomy in Malignant MCA Infarction (DECIMAL) trial,\textsuperscript{54} the Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery (DESTINY) trial,\textsuperscript{55} and Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial (HAMLET)\textsuperscript{56} - confirmed the mortality benefits of decompressive hemicraniectomy compared to best medical management in patients with malignant MCA infarction younger than 60 years of age but, individually, did not demonstrate significantly improved functional outcomes in survivors. A pre-planned merged analysis of the three trials including the 93 patients in whom treatment was initiated within 48 h of stroke onset reported that hemicraniectomy was associated with a significantly lower 12-month mortality compared to conservative management (22\% vs. 71\% respectively, p<0.0001; absolute risk reduction 50\%), and also a higher proportion of patients with favourable outcomes (mRS 0-4 vs. 5 or death).\textsuperscript{57} More patients who underwent hemicraniectomy survived with mRS ≤ 4 compared to those who received medical treatment (75\% vs. 24\%, p<0.0001; absolute risks reduction of 51\%), and 43\% survived with mRS 3 after surgery compared to 21\% of those after medical treatment (p=0.014; absolute risk reduction 21\%). This equates to numbers needed to treat of two for survival with mRS 4 or better, four for survival with mRS 3 or better, and two for survival irrespective of functional outcome. No patient in either group survived with no symptoms or no significant disability (mRS 0 or 1), and only 14\% and 2\% in the surgical and medical treatment groups respectively survived with slight disability (mRS 2). The effect of surgery was highly consistent across the three trials, and there was no difference in the benefits of surgery for any of the predefined subgroup analyses including age (older or younger than 50 years), presence or absence of aphasia, and earlier time to treatment.
(randomisation before or later than 24 h after stroke onset). A Cochrane systematic review incorporating the three original studies confirmed these summary findings, but cautioned that an overestimation of effect size could not be excluded because all trials were stopped early.58

Hemicraniectomy in more elderly stroke patients was investigated in the DESTINY II trial.59 Compared to medical treatment, hemicraniectomy within 48 h of symptom onset in patients with malignant hemispheric infarction resulted in lower mortality (33% vs. 70%, p < 0.001) but a higher proportion of severely disabled survivors (mRS 4-5) in patients aged between 61 and 82 years of age. 32% and 28% of survivors in the surgical group had moderately severe (mRS 4) and severe (mRS 5) disability respectively compared to 15% and 13% in the medical treatment group (both p<0.001). No patient survived with no or minimal disability (mRS 0 to 2), highlighting the grave prognosis of malignant MCA infarction in the elderly.

Decompressive hemicraniectomy is not associated with worse outcomes in patients with dominant compared to non-dominant hemisphere infarction.60 The outcomes in all age groups are also not influenced by prior administration of intravenous thrombolysis, but antiplatelet therapy does increase the risk of perioperative bleeding complications.61

Two recent systematic reviews have summarized recent clinical findings; irrespective of age, decompressive hemicraniectomy significantly reduces mortality and improves functional outcome in adults with malignant MCA infarction but with a non-significant increase in the risk of survival with major disability.6263 Optimum criteria for patient selection and timing of surgery for malignant hemispheric infarction are yet to be defined.58

**Decompressive craniectomy in other conditions**
Decompressive craniectomy has been used to manage intractable intracranial hypertension in other neurological conditions, but the evidence base is limited compared to that for TBI and AIS (table 3).

Intracranial hypertension is associated with increased mortality in patients with poor grade aneurysmal subarachnoid haemorrhage (SAH) but the relationship between raised ICP and outcome in survivors remains unclear, possibly because ICP has not historically been monitored routinely after SAH. While a recent systematic review and meta-analysis concluded that surgical decompression is associated with high rates of death and unfavourable functional outcome in patients with poor-grade SAH, lack of control groups in the majority of the (low quality) studies included in this review means that considerable uncertainty remains about the effects of craniectomy compared to other ICP-lowering interventions.

Up to one third of patients with spontaneous intracerebral haemorrhage (ICH) develop mass effect and raised ICP. In the acute phase after haemorrhage (< 24 - 48 h) this is usually related to hematoma expansion, but ICP increases beyond 48 hours are primarily related to extension of peri-hematoma edema. The surgical management of ICH remains controversial, but decompressive craniectomy with or without hematoma evacuation might reduce mortality in patients with large supratentorial haemorrhage, significant midline shift and refractory intracranial hypertension. Definitive recommendations about the relative merits and risks of surgical decompression after ICH (beyond evacuation of the hematoma in appropriate cases) cannot be made because of the limited number of (usually retrospective) studies with small numbers of patients.
Thrombosis of cerebral veins and/or dural venous sinuses can result in large increases in ICP because of obstructed venous outflow or venous infarction-related mass effect or haemorrhage. Current guidelines recommend consideration of decompressive craniectomy in patients with thrombosis-related neurological deterioration and significant mass effect despite the need to interrupt therapeutic anticoagulation to facilitate surgery. There is no evidence to guide the timing of anticoagulation resumption after decompressive craniectomy, so decisions should be made on an individual basis balancing the risks of post-operative bleeding against those of thrombosis extension of recurrence. Low rates of poor outcomes after decompressive craniectomy for cerebral venous thrombosis-related ICP elevations are reported despite poor neurological status before surgery. Case reports and small case series have also described the use of decompressive craniectomy to manage intracranial hypertension after encephalitis and acute disseminated encephalomyelitis but, again, only limited conclusions can be drawn because of the very small number of patients studied.

**Ethical considerations**

While there is unequivocal evidence that decompressive craniectomy is effective in reducing critically raised ICP and mortality, particularly in the context of TBI and malignant MCA infarction, there remain substantial questions regarding functional outcomes and quality of life in survivors. This raises complex ethical issues which are not unique to decompressive craniectomy but common to all interventions which reduce mortality at the risk of poor outcomes in survivors.

Survival with some degree of independence (moderate disability or better) has been the conventional definition of favorable outcome in brain injury studies, but recent clinical trials have used mRS 4 or better to define favorable outcome after AIS and GOS-E 4 or better
after TBI. This has important implications. Although the RESCUEicp study reported overall favorable outcomes of 42.8% and 34.6% in the surgical and medical groups respectively, the proportion of patients who recovered with a degree of independence (GOS-E 3 or better) was only 26.6% and 27.4% respectively.\(^4\) Similarly in the merged analysis of the three European stroke studies, the ‘headline’ rates of favorable outcomes were 75% and 24% in the hemicraniectomy and medical treatment groups respectively, whereas the proportion of patients surviving with only moderate disability or better (mRS 1-3) was 43% and 21% respectively.\(^5\) In more elderly patients, the potential for outcome with minimal disability is even less likely; only 7% and 3% of patients aged between 61 and 82 years survived with moderate disability or better in the surgical group and medical treatment groups in the DESTINY II trial.\(^6\) It is also important to appreciate that the different outcome assessment methods used in stroke and head injury studies represent very different levels of disability. GOSE-4 describes a state in which an individual is independent at home whereas individuals categorized as mRS 4 are unable to walk or attend to their own bodily needs without assistance. The justification for using GOS-E 4-8 or mRS 0-3 to define favorable outcome is that disability-free survival is unlikely after severe acute brain injury,\(^7\) and this approach is concordant with current recommendations.\(^8\) Notwithstanding the scientific validity, it is not certain that the degree of disability defined as ‘favourable outcome’ in recent clinical trials would be considered a satisfactory outcome by patients and their families.

While individual attitudes to levels of disability vary considerably, it is overall quality of life (rather the functional outcome in isolation) that is probably more important to many individuals. Patients’ perceptions of personal health, well-being, and satisfaction with life are often discordant with their objective health status. Many individuals appear to adapt to life-changing events and subsequently accept a degree of disability that they would previously
have judged to be unacceptable. In a personal view, a cardiac anesthesiologist outlined his own experiences of a massive MCA infarction and decompressive craniectomy. He observes that, while his post-stroke status seven years after the event is neither the life he previously enjoyed nor the one he envisioned for his fifties, it is still a life worth living. This case also illustrates the critical importance of intensive rehabilitation strategies in maximizing stroke outcomes, and the challenges faced by individuals and their families of engaging with potentially life-long therapy. A systematic review of 16 studies confirmed that the majority (77%) of patients and their families or caregivers were satisfied with life after hemicraniectomy for MCA infarction and would choose to undergo surgery again despite high rates (47%) of moderately severe disability, depression and overall reduction in quality of life. These data should however be interpreted with caution because of significant variability in study design, patient eligibility criteria, timing of surgery, and methods of outcome assessment in the studies included in the review. In a study investigating outcomes after severe TBI, the majority of 39 patients (or their next of kin) who had survived with severe disability for more than three years after decompressive craniectomy also indicated that they would have agreed to surgery even if they had been aware of the eventual outcome.

Clinicians’ attitudes to disability also vary, and may be very different to those of their patients. In the DESTINY-S study, a multicenter, international, cross-sectional survey of physicians involved in the treatment of patients with malignant MCA infarction, only 38% of 1,860 respondents considered mRS 4 or better to represent favorable outcome; the majority (79.3%) believed that mRS 3 is a more appropriate definition. The involved hemisphere was cited as a major factor influencing treatment decisions by 47.7% of respondents, resulting in substantial differences in the proportion of physicians who would recommend
decompressive hemicraniectomy in dominant versus non-dominant hemispheric infarction (46.9 vs. 72.9% respectively). Geographic region, base medical specialty and degree of experience were factors influencing physicians’ opinions of acceptable levels of disability and their treatment recommendations. In association with their personal views, differences in interpretation of clinical studies or failure to review outcomes beyond those highlighted in the abstracts might result in some physicians not offering decompressive craniectomy, or framing informed consent discussions in a way that reflects their individual biases, thereby denying an effective intervention to a patient who might benefit from it.81 On the other hand, the dismal outcome of untreated refractory intracranial hypertension may drive others to recommend surgery to every patient in order to give a chance of survival with reasonable functional outcome to a few. The importance of shared decision making in discussions about potential outcomes of therapeutic options, prolonged recovery times and potential post-procedure quality of life cannot be over-estimated.82

Future directions
The results of recent clinical trials have provided important clinical information about the role of decompressive craniectomy as a means to control intractable intracranial hypertension in severe TBI and AIS, but its benefits and risks remain highly uncertain. The total number of patients currently randomized into clinical trials is relatively small, and further studies incorporating standardized design and assessment methodologies are required to clarify the nuances of patient selection for decompressive craniectomy in different pathologies and identify more refined clinical decision-making tools.83 In addition to considering ICP thresholds, future studies should investigate monitored changes in cerebral blood flow, oxygenation and metabolism that might assist clinical decision making, and further define the role of decompressive craniectomy for the treatment of intractable intracranial
hypertension. Systematic investigation of the long-term outcome impact of the complications of cranioplasty is also required.

In addition, well-designed observational studies should be undertaken to provide better understanding of how competent individuals feel about survival with severe disability.77 These should include prospectively collected information from patients who may become candidates for decompressive craniectomy about their attitudes and advance wishes in relation to likely outcomes, and retrospective assessments of actual outcomes and how these relate to pre-intervention opinions.73

While decompressive craniectomy should considered as a treatment option in all appropriate patients, given the outstanding uncertainties about patient selection and outcomes it should not be offered as a routine intervention for intractable intracranial hypertension.11,85 Decisions to recommend decompressive surgery must be made not only in the context of its clinical indications but also after consideration of an individual patient’s preferences and quality of life expectations.

References


84. Lazaridis C, Czosnyka M. Cerebral blood flow, brain tissue oxygen, and metabolic effects of decompressive craniectomy. Neurocrit Care 2012; 16: 478-84

## Table 1

### Tiered treatment of intracranial hypertension

Complications of treatment increase from tier 1 through 4 level interventions

<table>
<thead>
<tr>
<th>Tier</th>
<th>Intervention</th>
<th>Risks/considerations</th>
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<tbody>
<tr>
<td>1</td>
<td>Elevate head of bed to 30°</td>
<td>Hypotension</td>
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<tr>
<td></td>
<td>Mechanical ventilation to maintain oxygenation and PaCO₂ 35-40 mmHg</td>
<td>Hypotension, propofol infusion syndrome</td>
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<td></td>
<td>Normovolemia</td>
<td>Surgery-associated risks, post-operative hemorrhage, cerebral edema</td>
</tr>
<tr>
<td></td>
<td>Propofol (2 - 4mg.kg⁻¹.hr⁻¹)</td>
<td>Specific drug side effects</td>
</tr>
<tr>
<td></td>
<td>Timely evacuation of intracranial mass lesions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treatment of seizures</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Increase sedation</td>
<td>Hypotension, propofol infusion syndrome</td>
</tr>
<tr>
<td></td>
<td>Neuromuscular blockade</td>
<td>Myopathy, neuropathy</td>
</tr>
<tr>
<td></td>
<td>Hyperosmolar agents</td>
<td>Hypotension, hyperosmolarity</td>
</tr>
<tr>
<td></td>
<td>Mannitol</td>
<td>Optimal osmolar load unknown</td>
</tr>
<tr>
<td></td>
<td>Hypertonic saline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normothermia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cerebrospinal fluid drainage via an external ventricular catheter</td>
<td>Risks of external drain insertion including bleeding and infection</td>
</tr>
<tr>
<td>3</td>
<td>Induced hypertension to increase cerebral perfusion pressure</td>
<td>Acute lung injury secondary to vasopressors and overzealous fluid resuscitation</td>
</tr>
<tr>
<td></td>
<td>Moderate therapeutic hypothermia</td>
<td>Arrhythmia, infection, fluid &amp; electrolyte abnormalities</td>
</tr>
<tr>
<td></td>
<td>Short-term, moderate hyperventilation (PaCO₂ 30-35 mmHg)</td>
<td>Cerebral ischemia</td>
</tr>
<tr>
<td>4</td>
<td>Barbiturates</td>
<td>Hypotension, increased duration of mechanical ventilation, infection</td>
</tr>
<tr>
<td></td>
<td>Decompressive craniectomy</td>
<td>Bleeding, infection, risk of survival with poor outcome</td>
</tr>
</tbody>
</table>
Table 2
Summary of absolute outcomes reported in the RESUCEicp trial

<table>
<thead>
<tr>
<th>Outcome category (GOS-E)</th>
<th>6 month outcome</th>
<th>12 month outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgical group (n=201)</td>
<td>Medical group (n=188)</td>
</tr>
<tr>
<td>1: dead</td>
<td>54 (26.9%)</td>
<td>92 (48.9%)</td>
</tr>
<tr>
<td>2: vegetative state</td>
<td>17 (8.5%)</td>
<td>4 (2.1%)</td>
</tr>
<tr>
<td>3: lower severe disability</td>
<td>44 (21.9%)</td>
<td>27 (14.4%)</td>
</tr>
<tr>
<td>4: upper severe disability</td>
<td>31 (15.4%)</td>
<td>15 (8.0%)</td>
</tr>
<tr>
<td>5: lower moderate disability</td>
<td>20 (10.0%)</td>
<td>19.0 (10.1%)</td>
</tr>
<tr>
<td>6: upper moderate disability</td>
<td>27 (13.4%)</td>
<td>18.0 (9.6%)</td>
</tr>
<tr>
<td>7: lower good recovery</td>
<td>5 (2.5%)</td>
<td>6 (3.2%)</td>
</tr>
<tr>
<td>8: upper good recovery</td>
<td>3 (1.5%)</td>
<td>7 (3.7%)</td>
</tr>
</tbody>
</table>

GOS-E, extended Glasgow outcome score
### Table 3

**Indications for decompressive craniectomy for the treatment of intracranial hypertension refractory to tiered medical therapy**

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Indications</th>
<th>Outcomes compared to medical therapy</th>
<th>Current evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Traumatic brain injury</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary decompression</td>
<td>Actual or anticipated brain swelling after evacuation of ASDH</td>
<td>Trend toward lower mortality and morbidity</td>
<td>Case series&lt;br&gt;Nonrandomized cohort study&lt;br&gt;Randomized controlled trial on-going</td>
</tr>
<tr>
<td>Secondary decompression</td>
<td>Second-tier ‘neuroprotective’ intervention</td>
<td>Not superior in patients with diffuse injury</td>
<td>Randomized controlled trial&lt;br&gt;Systematic reviews and meta-analyses</td>
</tr>
<tr>
<td></td>
<td>Last-tier therapy for refractory intracranial hypertension</td>
<td>Lower mortality but risk of survival with higher rates of severe disability</td>
<td>Randomized controlled trials&lt;br&gt;Systematic reviews and meta-analyses&lt;br&gt;Treatment option in consensus guidelines</td>
</tr>
<tr>
<td><strong>Acute ischemic stroke</strong></td>
<td>‘Malignant’ infarct-associated cerebral edema</td>
<td>Lowers mortality in all age groups</td>
<td>Controlled case series&lt;br&gt;Randomized controlled trials&lt;br&gt;Systematic reviews/meta-analyses&lt;br&gt;Recommended by consensus guidance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Improved functional outcomes in patients younger than 60 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Higher incidence of survival with moderate to severe disability in patients older than 60 years</td>
<td></td>
</tr>
<tr>
<td><strong>Subarachnoid haemorrhage</strong></td>
<td>Large intracerebral hematoma or space occupying cerebral edema</td>
<td>Possible reduced outcomes and improved functional outcomes</td>
<td>Large case series</td>
</tr>
<tr>
<td>Condition</td>
<td>Clinical Features</td>
<td>Outcome</td>
<td>Study Design</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>------------------------------------</td>
</tr>
<tr>
<td>Spontaneous intracerebral haemorrhage</td>
<td>Hematoma expansion or perihematoma edema causing rapid neurological deterioration</td>
<td>Limited evidence of reduced mortality and improved functional outcomes</td>
<td>Small retrospective studies</td>
</tr>
<tr>
<td>Cerebral venous sinus thrombosis</td>
<td>Space-occupying edema and neurological deterioration</td>
<td>Good functional outcomes in selected patients</td>
<td>Uncontrolled studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Systematic review</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Recommended by clinical guidelines</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>Life threatening cerebral edema and imminent herniation</td>
<td>Good recovery and long-term outcome reported but very limited data</td>
<td>Case reports</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Clinical review</td>
</tr>
<tr>
<td>Acute disseminated encephalomyelitis</td>
<td>Life-threatening cerebral edema</td>
<td>Life-saving in patients with brain herniation</td>
<td>Single case reports</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No reliable functional outcome data</td>
<td></td>
</tr>
<tr>
<td>Fulminant hepatic failure</td>
<td>Potential application in severe cerebral edema</td>
<td>No data</td>
<td>Animal studies only</td>
</tr>
</tbody>
</table>